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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte AVI ASHKENAZI, DAVID BOTSTEIN, LUC DESNOYERS, DAN L. EATON, NAPOLEONE FERRARA, ELLEN FILVAROFF, SHERMAN FONG, WEI-QIANG GAO, HANSPETER GERBER, MARY E. GERRITSEN, AUDREY GODDARD, PAUL J. GODOWSKI, J. CHRISTOPTER GRIMALDI, AUSTIN L. GURNEY, KENNETH J. HILLAN, IVAR J. KLJAVIN, JENNIE P. MATHER, JAMES PAN, NICHOLAS F. PAONI, MARGARET ANN ROY, TIMOTHY A. STEWART, DANIEL TUMAS, P. MICKEY WILLIAMS, and WILLIAM I. WOOD

Appeal 2008-4086
Application 09/904,766
Technology Center 1600

Decided: December 31, 2008

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 44-46 and 49-52. Jurisdiction is under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to full-length polypeptide, also known as PRO269, having the amino acid sequence identified by SEQ ID NO: 96 (Spec. 40). PRO269 is described by Appellants as a polypeptide having a signal peptide sequence and transmembrane domain (*see* Spec. 159-160 and Figure 36). According to the Specification, PRO269 gene is amplified[1] by approximately 2-3.5 fold in 8 primary lung tumors and tumor cell lines (Spec. 230-234 & 222-223; Table 9; App. Br. 3). Based on this data, Appellants assert the PRO269 polypeptide is useful as a marker for cancer.

The claims stand rejected by the Examiner as follows:

1) Claims 44-46 and 49-52 under 35 U.S.C. § 101 for lack of a credible, specific, and substantial utility (Ans. 4);

2) Claims 44-46 and 49-52 under 35 U.S.C. § 112, first paragraph, because persons of ordinary skill in the art would not know how to use the claimed invention (Ans. 10).

Claim 44 is representative of the claimed subject matter and reads as follows:

> 44. An isolated polypeptide comprising:
> (a) the amino acid sequence of the polypeptide of SEQ ID NO: 96;
> (b) the amino acid sequence of the polypeptide of SEQ ID NO: 96, lacking its associated signal peptide;
> (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 96; or

[1] Example 92, in the Specification at page 222, line 26, to page 235, line 3, describes a "Gene Amplification assay" which measures the level at which a certain gene (DNA) is increased in copy number ("amplified") over its normal copy number in the genome.

> (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209397.

ISSUE

The asserted utility of the claimed PRO269 polypeptide is as a cancer marker. This utility is based on evidence in the Specification that PRO269 DNA is amplified in certain cancers (Spec. 230-234). Although there is no data in the Specification about the levels of the polypeptide encoded by PRO269 DNA, Appellants assert that there is a correlation between DNA amplification and polypeptide levels (App. Br. 5). Appellants's position is apparently that this correlation would have led to the reasonable expectation that the levels of PRO269 polypeptide would be increased in cancer and that therefore PRO269 polypeptide, which is claimed, would be useful as a cancer marker.

The Examiner's position is that persons of ordinary skill in the art would have had reason to doubt that amplification of PRO269 DNA would result in increased levels of the polypeptide encoded by the DNA.

The issue in this case is as follows: Would a person of ordinary skill in the art on the filing date of the application have reasonably believed that PRO269 polypeptide would be useful as a cancer marker?

PRINCIPLES OF LAW

"Enablement, or utility, is determined as of the application filing date." *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995).

> [T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. . . . Only after the PTO provides evidence showing that one of ordinary skill in the

> art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy*, 642 F.2d 430, 433.

In re Brana, 51 F.3d at 1566.

To fulfill the utility requirement under 35 U.S.C. § 101, a claimed invention must have a specific and substantial utility. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). A substantial utility is one that "show[s] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *In re Fisher*, 421 F.3d at 1371.

A specific utility is

> use which is not so vague as to be meaningless. Indeed, one of our predecessor courts has observed "that the nebulous expressions 'biological activity' or 'biological properties' appearing in the specification convey no more explicit indication of the usefulness of the compounds and how to use them than did the equally obscure expression 'useful for technical and pharmaceutical purposes' unsuccessfully relied upon by the appellant in *In re Diedrich*." *In re Kirk*, 376 F.2d 936, 941 (C.C.P.A. 1967). Thus, . . . an asserted use must also show that the claimed invention can be used to provide a well-defined and particular benefit to the public.

In re Fisher, 421 F.3d at 1371.

FINDINGS OF FACT

The PTO has the initial burden of challenging a patent applicant's presumptively correct assertion of utility. *In re Brana,* 51 F.3d at 1566. The

Examiner's case for lack of utility is based on the following facts which are supported a preponderance of the evidence:

1. The claims are directed to an "isolated polypeptide" comprising the amino acid sequence identified as SEQ ID NO: 96. The polypeptide is also referred to as "PRO269."

2. The Specification showed that PRO269 was amplified two-fold or more in 8 lung cancers, which was less than half of the cancer samples tested (Spec. 222:33-43 (Example 92); Spec. 222: 44 to Spec. 223: 2; 230-234; Ans. 5: 1-5; App. Br. 5), a fact which Appellants do not dispute.

3. There is no data in the Specification reporting the levels of PRO269 mRNA or PRO260 polypeptide encoded by the amplified PRO269 DNA.

4. There is an imperfect correlation between DNA amplification and the expression of the corresponding mRNA and polypeptide. The following references were cited[2] by the Examiner to support this conclusion:

5. *Pennica*[3] described experiments which determined that WISP-1 DNA was amplified in colon tumors and its RNA was over expressed in 84% of the tumors examined (*Pennica*, Abstract).

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[2] The Examiner also cited the Konopka (James B. Konopka et al., "Variable expression of the translocated *c-abl* oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients," 83 *Proc. Natl. Acad. Sci.*, 4049-4052 (1986) and Sen (Subrata Sen, "Aneuploidy and cancer," 12 *Current Opinion in Oncology*, 82-88 (2000) references. We did not rely on them in our analysis as they do not appear to contain information relevant to the issue in this case.

[3] Diane Pennica et al., "*WISP* genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," 95 *Proc. Natl. Acad. Sci.*, 14717-14722 (1998).

6. However, WISP-2 DNA, a different DNA, was also amplified in colon tumors, but *Pennica* reports that its RNA expression was reduced in 79% of the tumors studied (*Pennica*, Abstract).

7. *Hanna and Morin*[4] stated that a subset of tumors tested for HER2/neu showed a lack of protein over-expression associated with gene amplification (Hanna and Morin, at first page (unnumbered), col. 2, last ¶)

8. *Godbout*[5] states that "[i]t is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell" (Godbout, at 21167, col. 2).

9. *Godbout* states that ERBA and ERBB2 DNA are commonly amplified in breast cancers, but ERBA protein is not overexpressed (*id.*). "Similarly, three genes mapping to 12q13-14 (*CDK4, SAS*, and *MDM2*) are overexpressed in a high percentage of malignant tumors showing amplification of this chromosomal region, while other genes mapping to this region (*GADD153, GLI*, and *A2MR*) are rarely overexpressed in gene-amplified malignant gliomas" (*id*).

10. According to *Bea*,[6] gene amplification [of the BMI-1 gene] was identified in four MCLs [mantle cell lymphomas]. These tumors showed significantly higher levels of mRNA and protein expression compared with

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[4] Julie Sanford Hanna, Ph.D. and Dan Morin, M.D., "HER-2/neu Breast Cancer Predictive Testing," *Pathology Associates Medical Laboratories* (1999).

[5] Roseline Godbout et al., "Overexpression of a DEAD Box Protein (DDX1) in Neuroblastoma and Retinoblastoma Cell Lines," 273(33) *The Journal of Biological Chemistry*, 21161-21168 (1998).

[6] Silvia Bea et al., "*BMI-1* Gene Amplification and Overexpression in Hematological Malignancies Occur Mainly in Mantle Cell Lymphomas," 61 *Cancer Research*, 2409-2412 (2001).

other lymphomas with BM1-1 in germline configuration" (Bea, at 2411, col. 1).

Rebuttal

Appellants provide the following rebuttal arguments and evidence:

11. Appellants cite several references which they state establish that the "in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration, the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels" (App. Br. 6).

12. The Orntoft, Hyman, and Pollack articles[7] were published in 2002, which is after the filing date of the instant application.[8] Utility is determined as of the filing date. *In re Brana*, 51 F.3d at 1567. There is no evidence that the information in these references would have been available to persons of ordinary skill in the art on or before the application filing date. Thus, we shall not consider these references as rebuttal evidence.

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[7] Torben F. Orntoft et al., "Genome-wide Study of Gene Copy Numbers, Transcripts, and Protein Levels in Pairs of Non-invasive and Invasive Human Transitional Cell Carcinomas," 1.1 *Molecular & Cellular Proteomics*, 37-45 (2002); Elizabeth Hyman et al., "Impact of DNA Amplification on Gene Expression Pattern in Breast Cancer," 62 *Cancer Research*, 6240-6245 (2002); Jonathan R. Pollack et al., "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors," 99(20) *PNAS*, 12963-12968 (2002).

[8] The present application was filed Jul. 12, 2001 and is a continuation of USSN 09/665,350, filed Sept. 18, 2000, which claims the benefit of several provisional applications with 1997 filing dates ("Bib Data Sheet").

13. A declaration 37 C.F.R. § 1.132 by Dr. Polakis (Second Declaration of Paul Polakis, Ph.D, dated Mar. 29, 2006) is provided that states:

> [O]f the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue at the mRNA level, 28 of them (i.e., greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level.

(Second Polakis Dec. ¶ 5).

14. However, Dr. Polakis does not establish that such data would have been known or would have reflected the knowledge of persons of ordinary skill on or before the application filing date. As utility is determined as of the filing date, we shall not consider Dr. Polakis's rebuttal evidence as set forth in ¶ 5 (FF13) of his second declaration.

15. In the same declaration, Dr. Polakis also states increased levels of mRNA "are more often than not predictive of elevated levels of the encoded protein" (Second Polakis Dec. ¶ 6). However, this statement does not address the reasonable doubt raised by the Examiner as to whether *DNA amplification levels* are predictive of mRNA or polypeptide levels.

16. A declaration under 37 C.F.R. § 1.132 by Dr. Audrey Goddard (Declaration of Audrey D. Goddard, Ph.D, dated Jan. 16, 2003) was provided in which she stated that it was her

> considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology.

(Goddard Dec. ¶ 7). This statement does not address the reasonable doubt raised by the Examiner as to whether DNA amplification levels are predictive of mRNA or polypeptide levels.

17. In another declaration 37 C.F.R. § 1.132 by Dr. Avi Ashkenazi (Declaration of Avi Ashkenazi, Ph.D., dated Sept. 15, 2003), it is stated:

> If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over- expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan® PCR or the fluorescence *in situ* hybridization (FISH) assays – is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy.

(Ashkenazi Dec. ¶ 5)

18. Dr. Ashkenazi also states:

> However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

(Ashkenazi Dec. ¶ 6).

ANALYSIS

35 U.S.C. § 101

In making the utility rejection, the Examiner relied on evidence that there is an imperfect correlation between DNA amplification and expression levels of the encoded protein (FF4-FF10). That is, polypeptide levels do not always increase when the DNA which encodes the polypeptide is amplified. The evidence included scientific reports in which DNA amplification was associated with a change in expression levels, but also reports in which DNA amplification did not effect expression. In sum, the Examiner established that DNA amplification does not always affect the levels of a DNA's encoded product. Based on these findings and because there was no evidence in the Specification of the levels of PRO269 mRNA or polypeptide in the tumor samples in which the PRO269 DNA had been amplified (FF2-3), the Examiner properly concluded that (1) persons of ordinary skill in the art would have reasonably doubted that PRO269 DNA amplification would affect PRO269 polypeptide levels and (2) thus would also have reasonably doubted that the claimed PRO269 polypeptide would be a marker for cancer, the asserted utility in this case (*see* App. Br. 5: 17-19).

Appellants have not provided adequate evidence to rebut the finding (FF4) that DNA amplification does not always affect levels of the encoded polypeptide. Instead, Appellants argue:

> it is more likely than not, that increased DNA levels generally correlate well with increased mRNA levels (based on, for example, the teachings of supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc.), and further, increased mRNA levels generally correlate well with increased protein levels (the two Polakis Declarations and the recent Board decision).

(Reply Br. 4; *see also* App. Br. 12).

The fact that it is "more likely than not" that DNA amplification is associated with increased polypeptide levels, as asserted by Appellants, does not predict what the result would be for the claimed PRO269 polypeptide. The results for different cancers using different DNAs show that sometimes DNA amplification results in a change in polypeptide levels, but sometimes it does not. For example, Godbout shows that out of six genes examined in the amplified 12q13-14 chromosomal region, three were "rarely" overexpressed (FF9). There is no evidence in the record about the particular PRO269 DNA and what about it would have lead persons of ordinary skill in the art to expect its amplification would result in increased levels of the PRO269 polypeptide.

For that matter, it is unclear what Appellants mean by the phrase "more likely than not." Assuming that an event is "more likely" when it occurs more than 50% of the time, then Appellants have not presented sufficient evidence that DNA amplification was known to alter polypeptide levels more than 50% of the time as of the effective application filing date.

In his declaration, Dr. Avi Ashkenazi states that "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment" (Ashkenazi Dec. ¶ 6; FF18). Dr. Ashkenazi explains that this would allow for more "accurate tumor classification" and for treatment reasons (*id.*).

As for the assertion about "tumor classification", we consider such use not to be specific for PRO269, but to be characteristic of the general

class of polypeptides. In other words, knowledge of the expression levels of any protein within the tumor would be informative, but not a specific use for the particular polypeptide which is claimed. A "general utility that would be applicable to the broad class of the invention" is not sufficient to satisfy the utility requirement of Section 101. *Manual of Patent Examining Procedure* ("MPEP") § 2107.01(I)(A) (Revision 6, September 2007). *See Fisher*, 421 F.3d at 1372 ("The PTO's standards for assessing whether a claimed invention has a specific and substantial utility comport with this court's interpretation of the utility requirement of § 101.").

Dr. Ashkenazi also states that "absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product" (Ashkenazi Dec. ¶ 6: FF18). Our difficulty with this assertion of utility is that no information has been provided about PRO269 function to establish that it would or would not be a target for drug therapy.

The Ashkenazi declaration, rather than making a strong case for utility, is more speculative than certain about what PRO269 would be useful for. Dr. Ashkenazi appears to acknowledge that there is unpredictability about whether gene amplification would lead to over-expression ("If gene amplification results in over-expression" of the mRNA and protein), but states that even when there is no over-expression, the gene product would still be useful (Ashkenazi Dec. ¶¶ 5-6; FF17-18). In our opinion, such uncertainty about the specific utility for PRO269 is a fundamental defect in the as-filed application.

35 U.S.C. § 112, first paragraph

Claims 44-46 and 49-52 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to teach how to use the claimed invention. If a claim fails to meet the utility requirement of 35 U.S.C. § 101 because it is not useful, then it necessarily fails to meet the how-to-use aspect of the enablement requirement of 35 U.S.C. § 112, first paragraph. *In re Fouche*, 439 F.2d 1237, 1243 (CCPA 1971) (If "compositions are in fact useless, appellant's specification cannot have taught how to use them."); MPEP 2164.07 (Edition 8, August 2001; revised August 2006). Because we have found that the claims do not meet the utility requirement, we also are compelled to find that they do not meet the how to use requirement of 35 U.S.C. § 112.

CONCLUSION OF LAW

Based on the totality of the evidence, we conclude that a person of ordinary skill in the art on the filing date of the application would not have reasonably believed that PRO269 polypeptide would be useful as a cancer marker. Accordingly, we affirm the rejection of claim 44. Claims 45, 46, and 49-52 fall with claim 44 because separate arguments for their patentability were not provided. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Because we have found that the claims do not meet the utility requirement, we also are compelled to find that they do not meet the how to use requirement of 35 U.S.C. § 112, first paragraph. We therefore also affirm the rejection of 44-46 and 49-52 under § 112.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc

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